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Bezold–Jarisch reflex in sino-aortic denervated malnourished rats

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ABSTRACT

In this study we assessed the role of Bezold–Jarisch reflex (BJR) in the regulation of blood pressure (BP) of malnourished (MN) and control rats (CN) with sino-aortic denervation (SAD). Fischer rats were fed diets containing either 6% (MN) or 15% (CN) protein for 35 days after weaning. These rats underwent sham or SAD and catheterization of femoral artery and vein for BP measurements and drug injection. Phenylbiguanide (PBG 5 μg/kg, i.v.) for activation BJR, produced bradycardia (−317±22 bpm for CN vs. −372±16 bpm for MN) and hypotension (−57±4 mm Hg for CN vs. −54±6 mm Hg for MN. After SAD, MN rats had reduced hypotensive (−37±7 mmHg for MN vs. −82±6 mm Hg for CN) and bradycardic (−124±17 for MN vs. −414±20 bpm CN) responses to BJR activation. To evaluate the contribution of the parasympathetic component due to BJR for the fall in BP, methyl atropine bromide, was given between two injections of PBG (5 μg/kg) separated by 10 min each other. Both bradycardic (−216±21 bpm before and −4±3 bpm after for CN −226±43 bpm before and −9±20 bpm after for MN) and hypotensive (−42±4 mm Hg before and −6±1 mm Hg after for CN −33±9 mm Hg before and −5±2 mm Hg after for MN) responses were abolished in CN and MN groups. These data indicate that dietary protein malnutrition changes the relation between baroreflex and BJR required for maintenance of the BP during malnourishment.

1. Introduction

Protein malnutrition affects millions of children in whole world (United Nations, 2008). Experimental studies revealed that pre or postnatal nutritional manipulations may provoke changes in adult size, metabolism, blood pressure, glomerular hypertrophy and atherosclerosis (Lucas et al., 1997; Lucas, 1998; Monteiro et al., 2001). These diseases may be consequences of a set of "programming", in which a stimulus or insult at critical or sensitive period early in life results in physiological and long-term metabolic changes (Barker and Clark, 1997; Plagemann et al., 2000; Minana-Solis Mdel and Escobar, 2008). Changes in dietary intake may exert an important influence on cardiovascular regulatory system (Leon-Quinto et al., 1998; Ferreira et al., 2003). Several studies have shown that reduced protein intake alters cardiovascular homeostasis, affecting peripheral vascular resistance, renin secretion, renal hemodynamics and reflex control of blood pressure (Barker et al., 1990; Benabe et al., 1993; Martinez-Maldonado et al., 1993; Benabe and Martinez-Maldonado, 1998; Plagemann et al., 2000; Oliveira et al., 2004; Loss Ide et al., 2007; Penitente et al., 2007).

Reflex control of circulation depends not only on arterial baroreceptors or chemoreceptors, but also on receptors located in the cardiopulmonary region, whose reflexively controls the activity of specific sympathetic fibers (Verberne and Guyenet, 1992; Vasquez, 1994; Mark and Dunlap, 2008). The Bezold–Jarisch reflex (BJR) is evoked by activation of cardiopulmonary chemoreceptive afferents and causes hypotension, bradycardia and apnea (Thoren, 1979). Previous data from the literature show that the fall in blood pressure evoked by BJR activation in unanesthetized freely moving rats is secondary to the reflex evoked bradycardia, which is entirely dependent on an increase in the parasympathetic drive mediated by NMDA receptors activation in NTS (Chianca and Machado, 1996).

Baroreflex and BJR share not only afferent and efferent cardiovascular pathways, but also common central integrative areas (Zanchetti and Mancia, 1991; Chianca and Machado, 1994; Vasquez, 1994). Some studies indicate that cardiopulmonary reflex and baroreflex can interact with each other in a mutual inhibitory way (Koike et al., 1975; Kashihara et al., 2003). As shown previously, cardiovascular responses

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to BJR activation are significantly greater following sino-aortic denervation (SAD) (Chianca et al., 1997).

Previous studies from our laboratory indicate changes in arterial baroreflex (Tropia et al., 2001; Loss Ide et al., 2007) and increased sensitivity of the chemoreflex in malnourished rats (Penitente et al., 2007). Those findings suggest changes in the central control of blood pressure during the malnourishment, which may represent adaptive or compensatory adjustments to keep blood pressure close to levels compatible with survival. However, the mechanisms by which protein restriction lead to cardiovascular compromising and how adaptive changes take place to compensate for such disturbances is not known.

In the present study, we tested the hypothesis that protein malnutrition after weaning contributes to changes in the autonomic control of the cardiovascular system by the BJR pathway evaluating the cardiovascular responses evoked by phenylbiguanide (used to activate the BJR) in control and malnourished rats before and after baroreflex denervation.

2. Materials and methods

All the experimental procedures were conducted in accordance with the guidelines established by Brazilian Council for Animal Experimentation (COBEA) and were approved by the institutional committee for animal use (Protocol # 2009/12). Male Fischer rats were fed either regular (15% protein) or low-protein (6% protein) diets and water *ad libitum* just after weaning and housed in a controlled environment (24 °C) on a 12/12-hour dark–light cycle (lights on 7:00 AM and off 7:00 PM).

2.1. Animal model

After birth, the offspring were randomly handled in such a way that eight male puppies were kept per mother. Weaning period lasted for 28 days. Thereafter, 4 animals were put in each cage and received either control (15% protein) or low protein (6% protein) diets for 35 days. Diets were manufactured so that they were isocaloric (422 kcal/100 g of diet) and had the same salts and vitamins purports. Compositions of both control and low protein diets are described in Table 1.

2.2. Surgical procedures and protocols

Animals were divided in four groups: intact malnourished (Intact MN), intact control (Intact CN), sino-aortic denervated malnourished (SAD MN) and sino-aortic denervated control (SAD CN).

One day before the experiments, under ketamine (100 mg/kg) and xylazine (2 mg/kg) anesthesia, the rats underwent sino-aortic denervation (to remove arterial baroreceptors) or sham surgeries as previously described by Krieger (1964). In the same surgical session, polyethylene catheters were placed into the femoral artery (for arterial blood pressure recording) and femoral vein (for systemic drug administration). The catheters were tunneled subcutaneously and exteriorized on the back of the neck. At the end of the surgery, Pentabiotic (1000 UI/kg, Fort Dodge, Brazil) was given intramuscularly and the animals were housed in individual cages in the experimental room until the experimental day for recovery and adaptation.

At the day of experiment, the arterial catheter was connected to a pressure transducer MLT0699 (ADInstruments, Australia). The blood pressure wave signal was amplified by an ETH-400 (CB Sciences Inc. USA) amplifier and digitized at 200 Hz by an analog-to-digital converter system (PowerLab/400, ADInstruments, Australia). Blood pressure waves were recorded in Chart4 software (ADInstruments, Australia) which also derived, online, the mean arterial pressure (MAP) and heart rate (HR). For analysis purpose, MAP and HR were recalculated offline for better resolution and precision of these parameters.

2.2.1. Bezold–Jarisch reflex activation

After at least 30-min of cardiovascular recordings, the BJR was activated by intravenous administration of phenylbiguanide (PBG) at the dose of 5.0 μg/kg in all four groups of animals. The efficacy of the SAD procedure was evaluated by intravenous injection of phenylephrine (250 nmol/kg/min) or sodium nitroprusside (400 nmol/kg/min) for approximately three minutes using a ramp infusion with an infusion pump (Bi 2000, Insight Ltda, Brazil). The magnitude of the cardiovascular responses, i.e., bradycardia and hypotension, were quantified and compared across groups.

2.2.2. Evaluation of BJR after vagal blockade

In order to investigate the contribution of cardiac vagal component for the hypotension induced by BJR activation, PBG was injected i.v. in intact animals before (10 min) and after (15 min) i.v. injection of methyl-atropine bromide (106.7 nmol/kg). To establish the efficacy of muscarinic blockade in the heart, the cardiovascular responses to the i.v. injection of acetylcholine (26.7 nmol/kg) were evaluated before (15 min) and after (10 min) methyl-atropine bromide i.v. injection (Takakura et al., 2003).

2.3. Data analysis

Data were presented as means ± SEM. For statistical analysis, unpaired Student *t*-test, one-way analysis of variance test or two-way analysis of variance followed by *post-hoc* Bonferroni's test were used. Significant differences between groups were considered when the probability of type II error was smaller than 5%.

3. Results

After 35 days of protein restriction, we observed markedly lower body weight in malnourished rats compared to the control ones (77 ± 3 vs. 200 ± 4 g; $P<0.05$, unpaired Student's *t*-test). Table 2 summarizes baseline values for cardiovascular variables in all four groups experimented. Malnourished intact group had significantly higher HR

Table 1
Composition (g/100 g of diet) of both control and low protein diets (Tropia et al., 2001).

	Types of diet	
Components	Control	Low Protein
Casein	15	6
Cornstarch	70	79
Soy oil	8	8
Mineral mixture	5	5
Vitamin mixture	1	1
Fiber (cellulose)	1	1
Energy density (Kcal)	422	422

Table 2
Body weight, mean arterial pressure (MAP), heart rate (HR) and baroreflex gain (bpm/mm Hg) in control (intact and denervated) and malnourished (intact and denervated) animals.

	Control	Malnourished	Control	Malnourished
	Intact (n = 8)	Intact (n = 8)	SAD (n = 8)	SAD (n = 8)
Body weight (g)	200 ± 4	77 ± 3*	197 ± 3	82 ± 3*
MAP (mm Hg)	108 ± 2	106 ± 2	131 ± 7#	106 ± 2
HR (bpm)	376 ± 7	444 ± 17+	465 ± 15#	388 ± 17
Baroreflex gain (bpm/mm Hg)	−1.89 ± 0.15	−1.41 ± 0.19	−0.03 ± 0.17	-0.08 ± 0.24

Values are mean ± SEM. * vs. control group ($P<0.05$). # vs. control intact, malnourished intact and malnourished SAD ($P<0.05$); + vs. control intact ($P<0.05$). (One way ANOVA followed by Bonferroni's post-test). SAD = sino-aortic denervation.

values compared to control (445 ± 17 vs. 376 ± 7 bpm, $P<0.05$, unpaired Student's *t*-test). As expected, the control SAD group had higher MAP levels when compared to other groups (131 ± 6 vs. 108 ± 2; 106 ± 2; 106 ± 2 mm Hg; control SAD vs. control intact, malnourished intact and malnourished SAD, respectively, $P<0.05$, one-way ANOVA). The baroreflex responses to vasoactive drugs injected i.v. were markedly reduced in SAD animal when compared to intact animals (Table 2). No significant differences were found in baroreflex gain values between the groups of intact animals (Table 2).

Fig. 1 shows tracings illustrating changes in MAP and HR (panels A, B, C and D) following BJR activation by intravenous injections of PBG (5.0 μg/kg) in intact (CN and MN, panels A and B respectively) and denervated groups (SAD CN and SAD MN, panels C and D respectively). PBG injection induced bradycardia and hypotension in all groups (Fig. 1, panels E and F). SAD MN group showed reduced hypotensive response to reflex activation compared to SAD CN group (ΔMAP: −37 ± 7 vs. −83 ± 6 mm Hg, respectively; $p<0.05$; one-way ANOVA). In addition, control SAD animals showed greater hypotensive response compared to the three other groups (−83 ± 6 vs. −57 ± 4; −54 ± 6 and −37 ± 7 mm Hg; SAD CN vs. CN, MN and SAD MN, respectively; $P<0.05$; one-way ANOVA). However, when the changes in MAP relative to baseline levels were taken in consideration (*i.e.*, the percent change in MAP), the only difference remaining was between SAD MN and the other groups (34 ± 5 vs. 53 ± 4; 58 ± 6 and 64 ± 4%; MN SAD vs. CN, MN and SAD CN, respectively; $P<0.05$; one-way ANOVA) as illustrated in Fig. 2. The bradycardia evoked by BJR activation was significantly reduced in SAD MN compared to CN, MN and SAD CN (−124 ± 17 vs. −317 ± 22; −372 ± 16 and −414 ± 20 bpm,

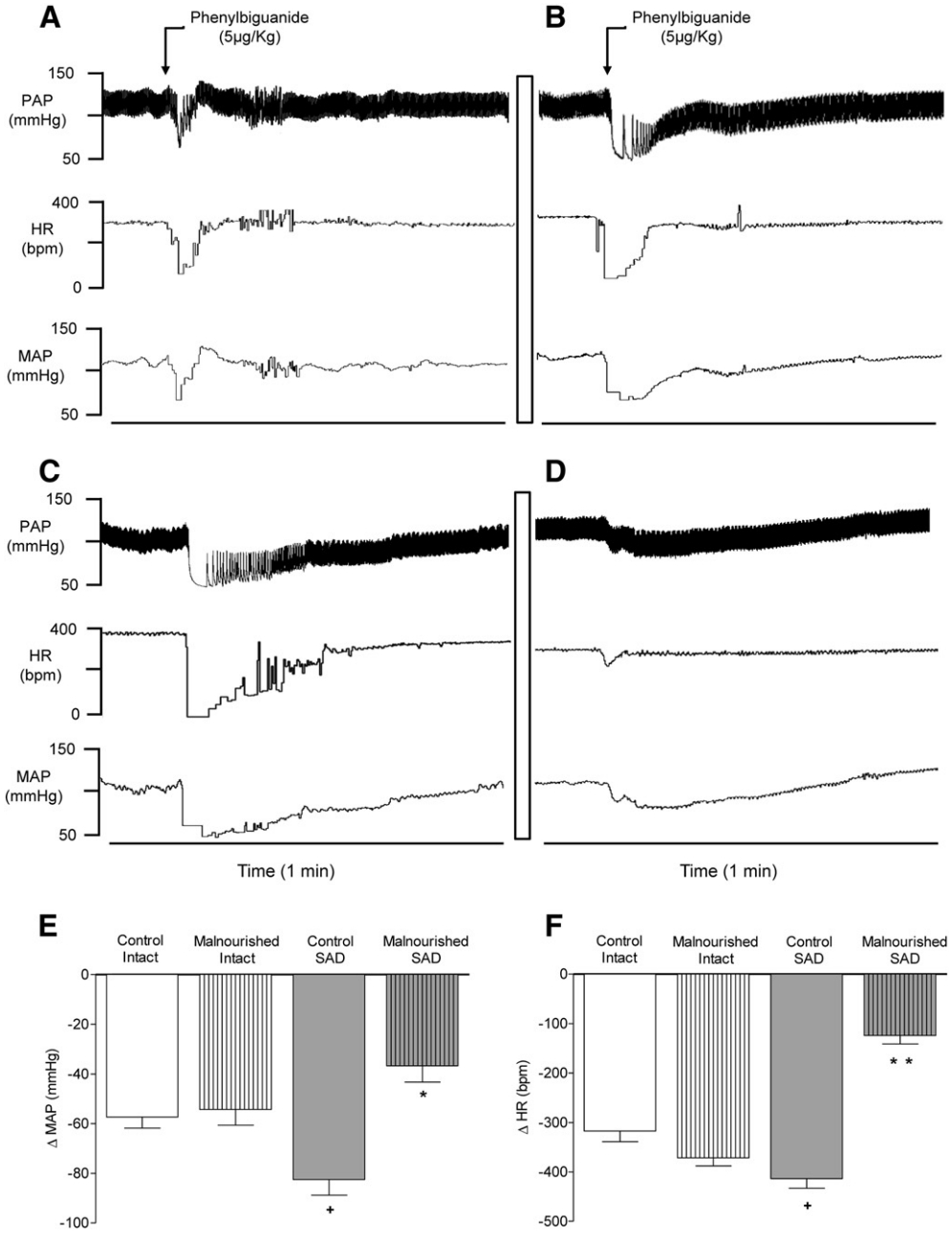

Fig. 1. Changes in arterial pressure and heart rate produced by activation of Bezold–Jarisch reflex in non-anesthetized rats. Representative tracings showing arterial pressure (AP), heart rate (HR) and mean arterial pressure (MAP) from: control intact and malnourished intact groups (A and B, respectively); control SAD and malnourished SAD (C and D, respectively). Changes in mean arterial pressure (MAP) and heart rate (HR) (E and F) to PBG (5.0 μg/Kg) in control [intact (n = 8) and denervated (n = 8)] and malnourished groups [intact (n = 8) and denervated (n = 8)]. * vs. control SAD, ** vs. control intact, malnourished intact and control SAD ($P<0.05$). $^{+}$ vs. control intact ($P<0.05$). (One way ANOVA followed by Bonferroni's post-test). MAP = mean arterial pressure; HR = heart rate; SAD = sino-aortic denervation.

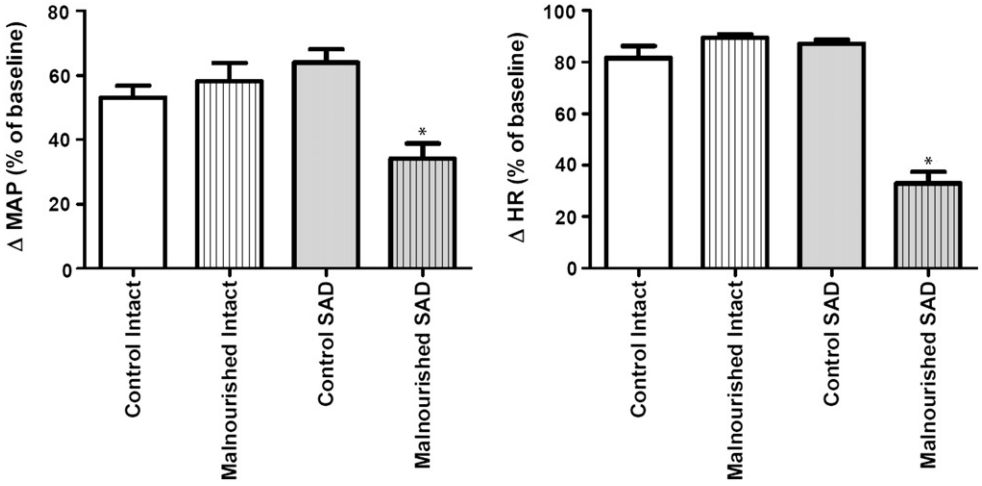

Fig. 2. Percent changes in blood pressure (Δ MAP) and heart rate (Δ HR) after the injection of PBG. Changes in mean arterial pressure (MAP) and heart rate (HR) to PBG (5.0 μg/kg) in control [intact (n = 8) and denervated (n = 8)] and malnourished groups [intact (n = 8) and denervated (n = 8)]. * vs. Control intact, Malnourished intact and Control SAD ($P<0.05$; One way ANOVA followed by Bonferroni's post-test). SAD = sino-aortic denervation.

respectively; $P<0.05$; one-way ANOVA) as shown in Fig. 1, panel F. The bradycardic response to BJR activation was also greater in SAD CN rats compared to the other groups as illustrated in Fig. 1 (-414 ± 20 vs. -318 ± 22; -372 ± 16 and -124 ± 17 bpm; SAD CN vs. CN, MN and SAD MN, respectively; $P<0.05$; one-way ANOVA) but, as summarized in Fig. 2, the relative changes in HR to baseline HR showed that the only difference remaining was between SAD MN and the other groups as observed for hypotensive responses (33 ± 4 vs. 82 ± 5; 89 ± 1 and 87 ± 2%; MN SAD vs. CN, MN and SAD CN, respectively; $P<0.05$; one-way ANOVA).

Since the hypotensive response to BJR activation was previously attributed to the bradycardic response in the literature (Chianca and Machado, 1994; Chianca et al., 1997), we assessed the contribution of the cardio-vagal reflex to hypotension developed during BJR activation in the four studied groups by two different methods. The first one evaluated the relationship between fall in blood pressure as a function of the fall in heart rate (ΔMAP/ΔHR) and the second one the residual hypotension after a pharmacological blockade of muscarinic cholinergic receptors in the heart by the methyl-atropine bromide. The relationship between hypotension and bradycardia revealed that SAD MN had a bigger index ΔMAP/ΔHR value compared to the other three groups (0.333 ± 0.060 vs. 0.190 ± 0.027; 0.147 ± 0.017 and 0.200 ± 0.014 mm Hg/bpm; MN SAD vs. CN, MN and SAD CN, respectively; $P<0.05$; one-way ANOVA), what suggests that hypotension in SAD MN rats is less dependent on bradycardic response than in the other groups (Fig. 3). The bradycardic (-261 ± 21 vs. -4 ± 3 bpm for CN and -226 ± 43 vs. -9 ± 20 bpm for MN; $P<0.05$; one-way ANOVA) and hypotensive (-42 ± 4 vs. -6 ± 1 mm Hg for CN and -33 ± 9 vs. -5 ± 2 mm Hg for MN; $P<0.05$; one-way ANOVA) responses to BJR activation were abrogated after intravenous injection of methyl-atropine bromide (106.7 nmol/kg) and recovered after a period of 2 h as shown in Fig. 4.

The dose of methyl-atropine bromide used in this study (106.7 nmol/kg) was determined by testing (data not shown) the smaller amount of methyl-atropine bromide capable of fully blockade the cardiovascular effects of the cholinergic agonist acetylcholine (26.7 nmol/kg). Acetylcholine was administrated before and after methyl-atropine bromide within a 15 minute interval. Intravenous acetylcholine caused significant reductions in HR (-25 ± 5 and -27 ± 5 bpm; CN and MN) and MAP (-47 ± 3 and -40 ± 5 mm Hg; CN and MN) for both groups. These MAP and HR effects were transient, lasted for 2 min and fully recovered to baseline levels within 30 to 90 s. Methyl-atropine bromide at 106.7 nmol/kg blocked MAP and HR changes elicited by acetylcholine in both groups (-4 ± 3 mm Hg and -3 ± 3 bpm for CN and -3 ± 3 mm Hg and -1 ± 2 bpm for MN; $P<0.05$ when compared with before methyl-atropine bromide; paired Student's *t*-test).

4. Discussion

The present study showed that protein malnutrition after weaning did not alter the cardiovascular responses evoked by intravenous injection of PBG. However, these cardiovascular responses were altered after baroreflex denervation of malnourished rats when compared with sino-aortic denervated control rats. Our data strongly suggest that dietary protein malnutrition changes the relation between baroreflex and BJR required for maintenance of the BP during malnourishment.

Clinical and experimental evidences have shown that protein malnutrition may affect several systems involved in homeostatic control (Martinez-Maldonado et al., 1993; Monteiro et al., 2001; Ferreira et al., 2003; Sawaya et al., 2003; Oliveira et al., 2004). In this study, baseline heart rate of malnourished rats was significantly higher than control animals, but no differences for MAP values were

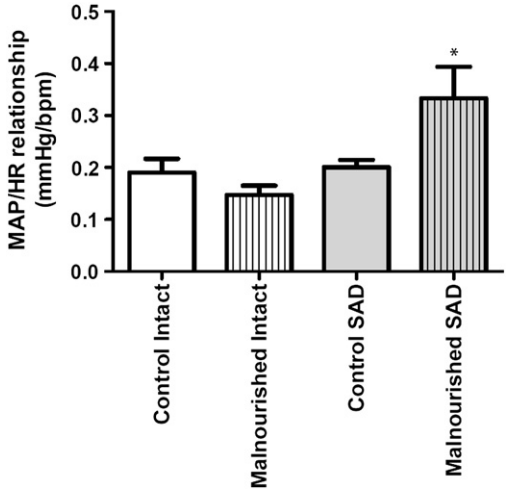

Fig. 3. ΔMAP/ΔHR relationship among the four groups studied. Changes in MAP as a function of changes in HR for Control intact (n = 8), Malnourished intact (n = 8), Control SAD (n = 8) and Malnourished SAD (n = 8) rats after BJR activation with PBG (5.0 μg/kg). * vs. Control intact, Malnourished intact and Control SAD ($P<0.05$; one way ANOVA followed by Bonferroni' post-test). SAD = sino-aortic denervation.

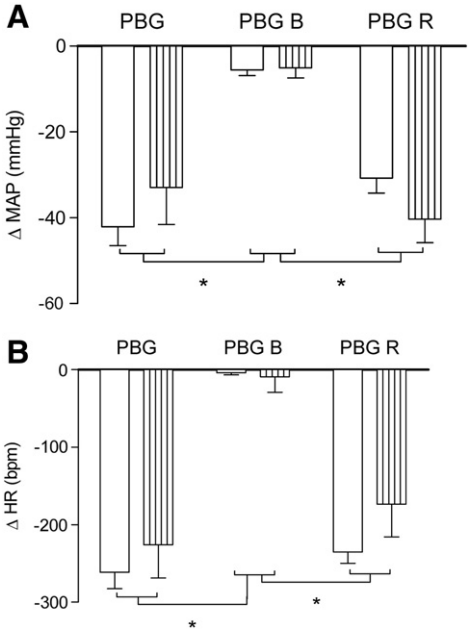

Fig. 4. Effects of vagal blockade with atropine methyl bromide on the hypotensive and bradycardic responses evoked by PBG. Changes in MAP (A) and HR (B) produced by injection of PBG (5.0 μg/kg) in control (n = 6) and malnourished (n = 6) rats (white and dashed bars, respectively). * vs. PBG B ($P<0.05$) (Two way ANOVA followed by Bonferroni's post-test). MAP = mean arterial pressure; HR = heart rate; PBG = phenylbiguanide; PBG B = phenylbiguanide 1 min after cholinergic blockade with atropine; PBG R = phenylbiguanide 60 min after cholinergic blockade with atropine.

found. This is in agreement with our recent report which also showed reduced sympathoinhibition to BJR activation in the same malnourishment model (Bezerra et al., 2011). A previous study reported that protein malnutrition causes changes in autonomic control, increasing sympathetic tone and decreasing parasympathetic activity to the heart (Leon-Quinto et al., 1998). These findings highlighted autonomic dysfunction in these animals which might lead to increased levels of heart rate.

The removal of aortic and carotid baroreceptors produces important changes in autonomic regulation of blood pressure with a marked increase in arterial pressure liability, but no sustained hypertension after denervation (Cowley et al., 1973; Jacob et al., 1988; Chianca and Machado, 1994; Krieger et al., 2006). In our results, we observed increased MAP and HR in control denervated rats along with normalization of heart rate of malnourished rats when compared to intact control rats. No changes in baseline MAP of malnourished rats were observed when compared with to intact control group. Krieger et al. (2006) also observed increased MAP and HR of denervated rats, at 6 and 24 h after denervation. These authors suggested that the acute increase of cardiovascular parameters may be due to increased renal sympathetic activity, with no change in plasmatic renin (Krieger et al., 2006). Other studies have reported that high values of MAP and HR found in rats after denervation return to normal within 48 h (Irigoyen and Krieger, 1998). Since our experiments were performed 24 h after SAD, we cannot suggest that these increased values can be characterized as hypertension. Different from control SAD animals, the levels of MAP and HR in malnourished SAD were not higher. On the opposite, denervation reduced baseline heart rate bringing it back to the levels observed in control intact rats. These data indicates that removal of baroreceptor inputs to the CNS of malnourished rats reveals a mechanism that normalizes the increased heart rate observed in these animals.

When activated with PBG, the BJR produced bradycardic and hypotensive responses similar in control intact and malnourished intact rats suggesting that protein malnourishment did not affect the reflex operation. On the other hand, removal of baroreceptors in malnourished rats reduced BJR responsiveness what is the opposite result found in denervated control rats, which exhibited increased responsiveness to BJR after SAD. The pivotal role for baroreflex in the short-term control of BP is well established (Krieger, 1964; Timmers et al., 2003). However, studies in humans and experimental models also have shown that the reflex control of BP probably involved not only baroreflex, but also cardiopulmonary afferent reflex pathways (Zanchetti and Mancia, 1991).

Previous studies reported that the hypotensive response evoked by BJR activation in conscious rats is entirely dependent on the bradycardic response (Chianca and Machado, 1996; Chianca et al., 1997; Leal et al., 2001). These studies indicate a possible key role of the parasympathetic drive for the cardiovascular response to BJR activation in conscious rats. In the present study, we observed the same relationship between BP and HR falls for control and malnourished intact rats but not for denervated malnourished rats. This finding suggests that the BJR-evoked sympathetic and parasympathetic responses are, somehow, dissociated in malnourished rats lacking the baroreflex. To test if that is a condition particular to malnourished rats lacking the baroreflex, the BJR was evoked during the muscarinic blockade with atropine in intact animals. The results revealed that intact rats presented the same pattern response for both groups. This result suggests that the bigger relation MAP/HR observed in denervated malnourished rats is a condition strictly related to the lack of baroreceptor inputs to CNS. The reason for this behavior of BJR in denervated malnourished rats is not fully understood and more studies are required for full unraveling of this phenomenon. However, we speculate that the malnourishment state may result in a bigger dependency of BJR by the baroreflex arc at CNS level so that the absence of the last may imply in less efficacy of the first. It is a worth hypothesis once the inhibition of medullary pathways involved in the control of baroreflex caused reductions in the responsivity to the BJR, associated with a concomitant blockade or attenuation of the arterial baroreflex (Verberne and Guyenet, 1992). Indeed, direct changes in the heart caused by protein malnutrition could contribute to the alterations in the BJR and baroreflex.

Our data show that protein malnutrition after weaning causes changes in the cardiopulmonary reflex regulation after baroreflex denervation. It may generate autonomic imbalances and negative impacts on cardiovascular homeostasis. The mechanisms involved in these changes remain to be further investigated.

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